REMARKS

Procedural History

A final rejection was mailed on March 8, 2004. Applicants filed a notice of appeal (with a petition for a two month extension of time) on August 5, 2004. On October 5, they filed both an amendment after final rejection and a request to correct inventorship. They were both denied entry by the advisory action mailed November 17, 2004.

On even date herewith, Applicants filed an RCE, requesting entry of the October 5 request to correct inventorship, but not of the October 5 amendment. The instant amendment is filed in lieu of the October 5 amendment, as it addresses certain issues raised by the advisory action. Nonetheless, its claims are virtually identical to those proposed on October 5, and hence it would be improper for the next action, if a rejection, to be made "final".

By this amendment, claims 18, 19, 23 and 26 are amended, claims 40 and 42 are cancelled, and claims 44 and 45 are added.

1. Enablement Issue

The enablement rejection is limited to dependent claim 26, which read as follows:

> The method of claim 23 for quantitative assay of MASP-2 or MASP-2 activity in biological samples.

Base claim 23 in turn recites

> A method for detecting mannin-binding lectin associated serine protease-2 (MASP-2), said method
> (a) obtaining a biological sample;
>
> (b) contacting said biological sample with a MASP-2 polypeptide specific binding partner that specifically binds MASP-2, thereby forming complexes of said binding partner with said MASP-2 polypeptide, if any,; and

> (c) detecting said complexes of MASP-2 and said specific MASP-2 binding partner, if any, as an indication of the presence of mannin-binding lectin associated serine protease-2 in said sample,
>
> where said binding partner is an antibody according to claim 19.

Since base claim 23 recites detecting MASP-2, not necessarily MASP-2 activity, claim 26 was improper under 35 USC 112 ¶4. We have amended it to delete "or MASP-2 activity" to overcome this problem, which of course incidentally moots the enablement issue. The advisory action concedes that the amendment in question overcomes the enablement rejection.

Applicants believe that they have enablement for a claim along the lines of, "The method of claim 23, further comprising detecting the enzymatic activity of said MASP-2 polypeptide in a sample". Note that this activity does not need to manifest itself <u>while</u> the MASP-2 is bound by the antibody of claim 19, that is, the MASP-2 can be released and <u>then</u> assayed for enzymatic activity. This meets the enablement argument set forth in the paragraph bridging pp. 2-3 of the rejection.

<u>2. Prior Art Issues</u>

2.1. Claims 18-19, 22-23 and 40 stand rejected under 35 USC 102(a) as anticipated by Thiel et al. (Nature 386:606; 1997).

There are several issues:

(1) Are the rejected claims entitled to the priority date of the April 3, 1997 provisional application? If so, then Thiel et al. (1997), which the Examiner concedes was published the same day, is not <u>prior</u> art.

(2) Is the inventorship entity for the relevant disclosure in Thiel et al. (1997) the same as the inventorship entity for the rejected claims? If so, then Thiel et al. (1997) is not the disclosure of the "invention of another" as required by 35 USC §102(a).

Independent claims 18 and 19 were directed to:

> 18. An antibody produced by administering an antigen comprising a mannin-binding lectin associated serine protease-2 (MASP-2 polypeptide) to an antibody producing animal.
>
> 19. An antibody that specifically binds to MASP-2.

Claim 18 has been amended to limit it to antibodies raised against human MASP-2. New claim 44 limits 19 to antibodies which specifically bind human MASP-2. Spelling errors in claims 18 and 23 have been corrected.

2.2. In the present action, the Examiner contends that the "chicken antibody raised against a bovine lectin preparation" does not satisfy the limitations of claim 18 because "it is not clear from the record that this 'bovine lectin preparation' is the same as an 'antigen comprising a mannan binding lectin associated serine protease-2' [MASP-2]".

The bovine lectin preparation in question was identified by P43, L17-18 as the one described in ref. 25 (Baatrup, et al., 1987), which is of record (reference "BM" in IDS). The bovine lectins and lectin-associated proteins were purified by zymosan affinity chromatography, gel permeation chromatography and SDS-PAGE.

The instant example 1 describes isolation of human MASP-2 from human plasma by a somewhat different procedure which included several carbohydrate affinity chromatography steps. The aforementioned anti-(bovine lectin preparation) chicken antibody recognized a 52 kDa protein band from the human isolate and the first 19 a.a. of the N-terminal were sequenced. The sequence was then used to raise the anti-N' MASP-2 antibody which the examiner concedes to recognize human MASP-2. This is persuasive evidence that the original chicken antibody was raised against a preparation containing the cognate bovine MASP-2 and in fact recognized the latter.

Since claim 18 has now been amended to require that the

antibody be raised against human MASP-2, we can no longer consider it to be the invention solely of the developers of the chicken anti-bovine MASP-2 antibody, Jensenius and Thiel. Hence, we have petitioned to add Willis, the sequencer of the N-terminal of human-MASP-2, as a joint inventor. Thiel et al. therefore does not disclose the invention of another with respect to claim 18.

2.3. Turning to claims 19 and 23 the Examiner contends that since the chicken antibody was raised against a (presumably heterogeneous) bovine lectin preparation, it would not be expected to meet the "specifically binds" limitation.

Since, at present, applicants have no evidence as to the specificity of that chicken antibody, they are compelled to accept the Examiner's position (office action, p. 4, first full paragraph) that the first antibody satisfying the limitations of claims 19 and 23 is the anti-N'-MASP-2 antibody referred to at P43, L22-26.

This antibody was raised against a 19 a.a. peptide corresponding to the first 19 a.a. of the human 52 kDa protein recognized by the anti-(bovine lectin preparation) antibody. The 52 kDa protein was sequenced by Anthony C. Willis, and the Examiner has taken the position (office action, p. 4, second full paragraph) that this sequencing was a "necessary inventive contribution" to claim 19.

Consequently, we filed, on August 5, 2004, a request to correct inventorship to add Anthony C. Willis as an inventor. We assume that this request will now be granted as of right.

This means that vis-a-vis claim 19, Thiel et al. (1997) can no longer be considered to disclose the invention of "another". To the extent that it discloses antibodies which specifically bind MASP-2, it is disclosing the invention of the present inventors. Hence, it does not qualify as 102(a) prior art against claim 19.

2.4. The Examiner asserts that because of their role in the determination of SEQ ID NO:2, which is recited in claim 40,

Vorup-Jensen, Reid, Eggleton, Schwaeble, Sim and Stover should have been named as inventors. This argument is moot as claim 40 has been cancelled. However, in cancelling claim 40, Applicants do not concede that the examiner's inventorship analysis of claim 40 is correct, they merely seek to narrow the issues in the case.

While the Examiner did not specifically discuss claim 42, it too recites SEQ ID NO:2, and has been cancelled for the same reason (and with the same caveat).

2.5. Three sets of declarations were enclosed with the October 27, 2003 amendment:

(1) nearly identical disclaiming declarations, each titled "Discovery of MASP-2", executed by Vorup-Jensen, Schwaeble, Laursen, Poulsen, Willis, Eggleton, Hansen, Holmskov and Reid;

(2) a declaration by Jensenius only, titled "Declaration Under Rule 1,32" [sic, "1.132"], executed October 18, 2003, and focusing on the contributions of Stover; and

(3) identical declarations by Jensenius and Thiel, again titled "Declaration Under 1,32" [sic, "1.132"], executed October 27, 2003, and focusing on the contributions of Willis.

The March 8, 2004 office action correctly states (top of page 5) that the disclaiming declarations do not contain a statement under 18 USC 1001 and hence do not comply with the formal requirements of 37 CFR §1.68.[1]

There is no such problem with the October 18 and October 26 declarations, which fully comply with 37 CFR §1.68.

The November 17, 2004 advisory action faulted our August 5 submission for failing to address the 18 USC 1001 problem. We did not need to address that problem because we did not need to rely on the disclaiming declarations. For example, the October

[1] Consequently, it was improper for the Examiner to reply upon them in deciding who made an inventive contribution to claim 40, see page 4 of the March 8, 2004 office actin.

18, 2003 Katz-type declaration, which contained an 18 USC 1001 statement, asserted in section 3 that Cordelia Stover "(and the other omitted co-authors) did not make an inventive contribution to the [then] claims of the above-identified application".

Moreover, the Examiner had only asserted (1) that Willis was a joint inventor as to the main claims, and (2) that certain other individuals were joint inventors as to claim 40. The August 5 response mooted both these issues, by adding Willis as an inventor and by cancelling claim 40. There was therefore no need to discuss the formal deficiencies in the disclaiming declarations because the Examiner had already concluded that the facts only necessitated naming Stover et al. if a pending claim recited SEQ ID NO:2. Cancellation of claims 40 and 42 moots that conclusion.

For the sake of good order, we have melded the three prior sets of declarations into a single new Katz-type declaration, updated to take into account, e.g., our revised position on whether Willis is an inventor. The executed Third Declaration of Jensenius and Second Declaration of Thiel are enclosed herewith.

2.6. In the May 27, 2003 office action, p. 4, the Examiner asserted that the provisional application is a verbatim copy of Thiel et al. (1997) (it isn't) and does not support the instant claims (it does). We are not sure whether the Examiner is still of this opinion, and hence address the issue here.

Reviewing the disclosure of the provisional application, we find disclosure of

(1) chicken antibody-raised against a bovine lectin preparation recognized a human 52 kDa protein (MASP-2) as well as MBL (32 kDa).

(2) The 19 N-terminal AAs of this 52 kDa band were determined.

(3) A rabbit polyclonal antibody (anti-N'-MASP-2) was made against a peptide corresponding to the amino terminal (AAs 1-19) of the 52 kDa protein (MASP-2) and was

shown to recognize a 52 kDa polypeptide and a 20 kDa polypeptide[2] (P43, L13-17; Fig. 1, lane 1.) (Ex. 1, P43, L13-17; P44, L9-10 and 18-22). This antibody was used in a Western blot (Ex. 3; P45, L19-21; P50, L10-12).

(4) The identities of 88 residues of MASP-2 (52 kDa band) were then determined directly.

(5) The complete AA sequence of MASP-2 was subsequently determined by cDNA sequencing; degenerate sense and antisense primers based on two known peptides (P46, L6-9).

(6) Chicken polyclonal antibody (anti-C' MASP-2) was raised against a mixture of two peptides corresponding, respectively, to AAs 505-523 and 538-556 in the C-terminal region of MASP-2 (Ex. 2; P44, L22-25). It recognized a 31 kDa polypeptide and a 76 kDa polypeptide (Ex. 1; P43, L28-P44, L4; Fig. 1, lines 3 and 4).

(7) The preparation of polyclonal and monoclonal antibodies against full-length MASP-2, or against other fragments of MASP-2 was suggested, but not then carried out. See P30, L26-P35, L19.

2.7. The Examiner asserted in the May 27, 2003 office action that "a mere disclosure of antisera against particular N and C terminal peptides cannot support claims to any kind of antibody against any portion of MASP-2" (para. bridging pp. 4-5).

This issue therefore reduces to whether it would have required undue experimentation to obtain antibodies against other epitopes of MASP-2 once a polyclonal antibody against the N-terminal epitope was available. The May 27, 2003 action assumed

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[2] We consider the 20 kDa polypeptide, a truncated form, to be within the meaning of "a human MASP-2". See P4, L24-26. Thus, an antibody which binds both the 20 kDa and 52 kDa polypeptides still can be said to specifically bind human MASP-2.

that the answer is negative, without any explicit review of the teachings of the specification or of the prior art.

It is unclear whether the Examiner still makes that assumption, so, in the interest of compact prosecution, we address that issue here.

Applicants do not contend that the preparation of antibodies against MASP-2 posed any special difficulties. The reason that their anti-(MASP-2) antibodies are novel is that applicants were the first to isolate MASP-2 itself (Prov. Appl. P3, L8-10).

As explained on P42, L23-P43, L13 of the provisional application, MASP-2 was isolated in sequenceable purity by a combination of (1) calcium-dependent mannan-sepharose affinity chromatography, (2) GlcNAc Sepharose affinity chromatography, and (3) preparative SDS-PAGE. The sequences of the amino terminal (41 amino acids) and of several tryptic fragments (27 a.a.; 12 a.a.; 8 a.a.) were determined; these are the sequences underlined in Fig. 6. See P48, L30-32.

Thus, it would have been easy to raise antibodies not only against MASP-2 (1-19), but also against the thus determined MASP-2 (20-41), MASP-2 (43-119), MASP-2 (362-373) and MASP-2 (395-402).

To raise antibodies against epitopes located elsewhere in MASP-2, it was not needful to know the complete AA sequence of MASP-2. All one needed was intact MASP-2 in a reasonably pure form. The procedure of Example 1 already provided MASP-2 in such form, and the anti-N'-MASP-2 antiserum could have been used to purify it further, if desired.

The techniques of making polyclonal and monoclonal antibodies are well known in the art, and are indeed discussed in great detail at P30, L26-P35, L19.

We believe that the above disclosure, by itself, is sufficient to fully enable the claims.

Thus far, in analyzing the question of basis for the claims in the provisional application, we have ignored the disclosure of the complete amino acid sequence in Ex. 4 and Fig. 6.

However, knowledge of this sequence allows one to (1) avoid purification of MASP-2 from plasma by instead producing MASP-2 recombinantly, and (2) predict the location of regions likely to be antigenic, "by criteria such as high frequency of charged residues", and of regions likely to contain epitopes unique to MASP-2, because they "lie outside of conserved regions". See P32, L31-P33, L1.

Thus, it is quite clear that even the provisional application (let alone the instant application) is fully enabling for the rejected claims.

Respectfully submitted,

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Enclosures
-Third Declaration of Jensenius
-Second Declaration of Thiel

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